UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:			
John Ong et al.		Art Unit:	1654
Appln. No.:	10/559,595	Examiner:	HA, Julie
Filed:	November 30, 2005	Atty. Docket:	0501US-UTLI
For:	*Novel Methods and Compositions for Enhanced Transmucosal Delivery of Peptides and Proteins*	Confirm. No.:	2750

REPLY BRIEF

Commissioner for Patents
Mail Stop Appeal Brief
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

In response to the Examiner's Answer mailed 12/9/09 Applicants submit the following Reply Brief.

35. U.S.C. 112, 2nd paragraph

The Examiner's Answer does not directly respond to the Applicant's explanation and argument provided in the Appeal Brief with respect to the rejection under 35 U.S.C. 112, second paragraph, but merely repeats at pp. 16-17 the allegations made in the final Office Action, that "there are not enough charged amino acids to reach a net charge that equals mono-anionic or neutral net charge, and be the same as the polyamino acids." (Examiner's Answer, p. 17, lines 1-3). This ignores the Applicant's explanation provided in the Appeal Brief at p. 7, where Applicant referenced relevant passages from the specification and the established case law stating that claims must be read in view of the specification of which they are a part. *Markman v. Westview Instruments, Inc.* 52 F.3d 967; 34 USPQ2d 1321 (Fed. Cir. 1995) (in banc) *aff'd*, 517

CERTIFICATE OF TRANSMITTAL UNDER 37 C.F.R. 1.8

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being electronically filed via EFS-Web at the United States Patent and Trademark Office, on the date shown below.

2-9-2010
Date of Deposit

Melissa K. Buckman

U.S. 370; 38 USPQ2d 1461 (1996). The meaning of the term "same net charge" is made clear at paragraph 23 of the specification (p. 8, lines 16-20) where it is stated:

> In one embodiment the peptide or protein has the same net charge as the polyamino acid at the pH of the composition. For example, at the pH of the composition both the protein and the polyamino acid have a net positive charge. In this situation, it is not necessary that the magnitude of the charge be identical, but only that the net charge be the same.[emphasis added]

Thus, when the claims are properly interpreted in view of the specification and using legal precedent, it is clear that the claims are not indefinite. It is clear that the claim language means that the protein or peptide and the polyamino acid both have a net positive charge or a net negative charge, and that the magnitude of that charge is not referred to in the claim. The rejection insists that both the protein or peptide and the polyamino acid must have the same magnitude of charge (e.g., +3, +10, etc). But this interpretation ignores the clear meaning set out in the specification and ignores established case law, and thus has no legal basis. (*Credle v. Bond*, 25 F.3d 1566; 30 USPQ2d 1911 (Fed. Cir. 1994) ("If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, the demands of 35 U.S.C. 112 are satisfied"); *Markman*. For all of these reasons the claims are not indefinite and the demands of 35 U.S.C. 112, second paragraph are met.

The Answer alleges that exendin-4 has 4 positively charged amino acids and 6 negatively charged amino acids and that "[t]his would give a net charge of -2, which is not the same as polyamino acids." (Examiner's Answer, p. 17, lines 10-14). But, as noted in the Examiner's Answer, the pI of exendin-4 is 5.3. Therefore, persons of ordinary skill in the art readily understand that at a pH of 4.5, exendin-4 will be positively charged, i.e., have a net positive charge. Persons of ordinary skill understand that the pI or "isoelectric point" refers to the pH value where the overall net charge of a macromolecule such as a peptide is zero, and at a pH above the isoelectric point the overall net charge of the peptide will be negative, whereas at pH values below the isoelectric point the overall net charge of the peptide will be positive. Therefore, at a pH of 4.5 the peptide and the polyamino acid are both positively charged, i.e., have the same net charge. For all of these reasons the claims are not indefinite and the requirements of 35 U.S.C. 112, second paragraph are met.

35 U.S.C. 102(b) – Rothbard

Applicant here references the allegations made in the Examiner's Answer, beginning at the last line of p. 17 and continuing onto p. 18.

First, Applicant notes that anticipation requires that every element of the claimed invention must be found in a single prior art reference, arranged as in the claim. *Brown v. 3M*, 265 F.3d 1349; 60 UPSPQ2d 1375 (Fed. Cir. 2001) (emphasis added). The Examiner's Answer alleges that Rothbard teaches biologically active protein, delivery-enhancing transporter, and biologically active agents in a suitable medium, such as water or a buffered aqueous solution, referencing paragraphs 26, 38, and 123 of Rothbard. The Answer alleges that since the bioactive peptide and cationic polyamino acid are formed in water or aqueous buffer they would inherently have the functionality and characteristics of the instantly claimed invention (Examiner's Answer, p. 4, lines 3-5).

Rothbard states clearly at paragraphs 44 and 45 that his compositions "are held in an ionic association, typically viewed as an ion pair" and that "the transporter will be positively charged and the biologically active agent will be negatively charged." (paragraph 45). The present claims recite that "the bioactive peptide or protein of interest has the same net charge as the cationic polyamino aicd at the pH of the composition." Therefore, as a matter of law, Rothbard does not anticipate the claims because all claim limitations are not satisfied by Rothbard. *Brown v. 3M*. Example 3, paragraph 181, also makes it clear that what is formed by Rothbard is a salt (i.e., the taxol has a negative charge and the heptamer of arginine has a positive charge). Rothbard is directed towards small organic acids such as taxol conjugates (e.g., Examples 1, 2, 3). While Rothbard's definition of "biologically active agent" can encompass proteins or polypeptides (paragraph 26), Rothbard provides no example or enablement for such a composition, and it is clear from the disclosure of Rothbard that such a protein or peptide (assuming, *arguendo*, that Rothbard could even enable such a composition) would have to be formulated at a pH to have a negative charge in order to fulfill the explicit requirements stated by Rothbard for the composition disclosed. Therefore, whatever else Rothbard discloses, it does not disclose a composition according to the present claims. And therefore, the reference does not

disclose a product "appearing to be substantially identical" to the claimed invention, as alleged in the Examiner's Answer (p. 18, lines 6-8).

The Examiner's Answer also re-states the rejection under 35 U.S.C. 102(a) as allegedly being anticipated by Defelippis et al. (WO 02/098348). The Examiner's Answer alleges that Defelippis discloses a composition at the same pH (about pH 5.0 to about 6.0 and below 5.0) comprising poly-arginine and exendin-4 and the use of acetate buffer." (Examiner's Answer, p. 18, last paragraph). First of all, Defelippis never discloses acetate buffer. The Answer apparently refers to the disclosure at p. 29, line 24, which discloses zinc acetate as an example of a zinc salt. This is disclosed for the purpose of adding zinc to the composition and does not function as a buffer. The disclosure at p. 27, lines 18-20 of Defelippis states that the GLP-1 compound and the basic polypeptide solution are buffered. The buffers disclosed include Tris, arginine, and phosphate (p. 26, lines 7-9) for the GLP-1 compound, and Tris, glycine, arginine, and phosphate for the basic polypeptide solution (p. 26, lines 23-26). Each of these buffers is appropriate for buffering in the high pH range, far above the pH 5.0 proposed by the Examiner. The buffer having the lowest pH range is phosphate, but even that is ineffective as a buffer below pH 5.8, and would not be selected even at that pH since it is has no real buffering capacity at such a pH. Thus, if the person of ordinary skill really wanted the solution of Defelippis at low pH, such person would not select phosphate either as a buffer. This is not surprising, since the disclosure of Defelippis is directed towards compositions having particles that are composed of GLP-1 and a basic polypeptide (p. 5, Summary). The particles are either crystalline or amorphous material or a mixture thereof (p. 23, lines 18-20). Thus, notwithstanding the disclosure pointed to by the rejection, the formulations disclosed by Defelippis are disclosed as having higher pH. Indeed, Defelippis calls his polypeptide solution a "basic polypeptide solution" (p. 26, line 23). Even using any of the buffers taught by Defelippis and lowering the pH to 5 would not yield the claimed composition, which recites a composition having a buffer with a "mono-anionic or neutral net charge." The Tris and arginine buffers taught by Defelippis are poly-cationic at pH < 5.0, and none of the buffers taught by Defelippis have buffering capacity at such pH. Therefore, the person of ordinary skill would never use these buffers. Therefore, Defelippis does not disclose the invention, and does not render it obvious either.

With respect to the allegation that Defelippis "teaches the same composition in the same pH range" and "therefore has the same characteristic as the instant claims" Applicant notes that Defelippis also teaches that his compositions precipitate upon administration and perform a protracted time action (Defelippis, p. 31, lines 17-21), which the claimed invention does not. This is verified by Figures 1 and 2 of the present application showing that the claimed compositions do not have this characteristic. Therefore, they are clearly not the same composition, because how molecular compositions are ordered can produce very different results. This is a further example of how the rejection is based in hindsight by selecting portions of the disclosure while ignoring other portions not supporting the rejection. As noted above, the compositions of Defelippis are particulate compositions, and in addition to not disclosing the buffer having a mono-anionic or neutral net charge at the pH of the composition, also fails to satisfy the claim requirement that the transmucosal absorption of the exendin is increased relative to the absorption of the exendin in the absence of the polyamino acid. The same arguments are applicable to the rejection under 35 U.S.C. 102(e) over Defelippis. For all of these reasons, Defelippis does not anticipate the claimed invention.

35 U.S.C. 103(a)

With respect to the rejection under 35 U.S.C. 103(a) over Young in view of Baichal and Ryser, Young discloses at paragraph 201 a formulation which lacks at least a polyamino acid. The rejection proposes to combine Baichwal with Young and thus allegedly arrive at the claimed invention. But Baichwal is not combinable with Young for reasons described in the Appeal Brief. That Young and Baichwal both mention mucosal delivery does not render them automatically combinable as suggested in the Answer (p. 21, top), since the principles involved in achieving mucosal delivery can conflict and vary widely, as they do here. Young discloses a liquid formulation at paragraph 201 containing exendin, acetate buffer, and mannitol. Baichwal discloses a solid tablet containing an active ingredient that is intended to provide a localized effect (Col. 2, lines 33-37). The tablets are intended for use in the oral cavity (Col. 7, lines 8-11).

Ryser states that molecules that are either excluded from or taken up poorly by cells can have their uptake increased if a conjugate of these molecules is formed by covalently bonding them to a cationic polymer (Col. 4, line 2). Ryser makes no disclosure regarding having cationic polymers simply included within a formulation. Ryser suggests the cationic polymer appears to serve as a transport carrier and that the conjugated molecule is transported through cell membranes in a much more effective manner than unconjugated molecules, thus requiring conjugation (Col. 4, lines 3-11). Furthermore, Ryser says nothing regarding the ability of any cationic polymer to facilitate transmucosal absorption. Ryser addresses transporting the molecules into cells, not across mucosal membranes – these are different physiological processes. Since Ryser does not disclose any information regarding transporting molecules across mucosal membranes, it is not very relevant to the present invention, which is directed towards transmucosal administration.

For these reasons, no prima facie case for obviousness has been made.

Closing

In view of the above the Applicant respectfully requests that the rejections be reversed and that the claims be passed to allowance (or examination continued beyond the elected species).

No fees are believed due with this filing because the Applicant previously paid both the Notice of Appeal and Appeal Brief fees under 37 CFR 41.20(b)(1) and (b)(2) on April 11, 2008, and having been once paid are not further due (MPEP 1204.01). However, if Applicant is in error and any fees are due, the USPTO is authorized to debit PTO Deposit Account # 01-0535 for said fees, as well as to credit back any refunds or overcharges.

Respectfully submitted

Feb. 9, 2010
Date

Richard San Pietro
Reg. No. 45,071

Amylin Pharmaceuticals, Inc.
9360 Towne Centre Dr.
San Diego, CA 92121

Direct: 858-754-4981
Fax: 858-552-1936
richard.sanpietro@amylin.com